



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07C 203/04, 201/02, 69/90, C07D 209/28	A1	(11) International Publication Number: WO 00/44705 (43) International Publication Date: 3 August 2000 (03.08.00)
<p>(21) International Application Number: PCT/EP00/00353</p> <p>(22) International Filing Date: 18 January 2000 (18.01.00)</p> <p>(30) Priority Data: MI99A000134 26 January 1999 (26.01.99) IT</p> <p>(71) Applicant (<i>for all designated States except US</i>): NICOX S.A. [FR/FR]; 45 Avenue Kléber, F-75116 Paris (FR).</p> <p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). GARUFI, Michele [IT/IT]; Via M. Marchesi De Taddei, 8, I-20146 Milano (IT).</p> <p>(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN DERIVATIVES</p> <p>(57) Abstract</p> <p>The invention describes a method for the synthesis of nitroxymethylphenyl esters of aspirin derivatives.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

SYNTHESIS METHOD OF NITROXYMETHYLPHENYL ESTERS OF ASPIRIN
DERIVATIVES

* * * * *

The present invention relates to an improved synthesis for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives.

These esters have interesting pharmacological and therapeutical properties; specifically they show an improved systemic and local tolerability, at the level of the gastric mucosa (WO 95/030641) and they are more effective as antithrombotic medicines (WO 97/16405).

It is known in the prior art that the (nitroxymethyl)phenyl esters of the aspirin derivatives are prepared by reacting (nitroxymethyl)phenol with the aspirin derivative in the acid form (WO 97/16405).

In particular the preparation of (nitroxymethyl)phenol is carried out starting from (hydroxymethyl)phenol through the following steps:

- reaction of phenol with HBr in an organic solvent to obtain (bromomethyl)phenol;
- reaction of (bromomethyl)phenol in an organic solvent with AgNO_3 to form (nitroxymethyl)phenol.

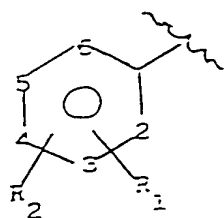
The synthesis of the (nitroxymethyl)phenol intermediate has the following drawbacks. The (bromomethyl)phenol is a chemically unstable and irritant compound. The nitroxy

derivative obtained from (bromomethyl)phenol is still an unstable compound, which must be purified before reaction with the acid chloride. The (nitroxymethyl)phenol may further decompose in a not controllable way; consequently in order to obtain, on an industrial scale, the compound with the required purity for the final esterification step, the purification processes normally used in laboratory organic syntheses cannot be employed.

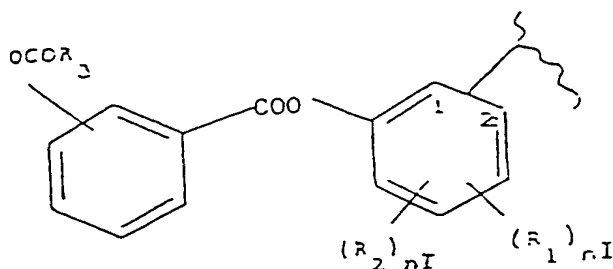
In conclusion the use of (nitroxymethyl)phenol in the synthesis of (nitroxymethyl)phenyl esters of aspirin derivatives is not industrially practicable.

It has been surprisingly and unexpectedly found by the Applicant that it is possible to synthesize (nitroxymethyl)phenyl esters of aspirin derivatives, and specifically (nitroxymethyl)phenyl esters of the N-acetylsalicylic acid, by synthetic reactions by which it can be avoided the use of the above mentioned phenol derivatives, and thus the purification steps of the intermediate compounds, obtaining the final products in good yields. Thus the new process is more advantageous than those of the prior art.

It is therefore an object of the present invention a new process for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives of formula $R-COOH$ wherein R is selected from one of the radicals having the following formula:



Ia)



Ib)

wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or alkyl C_3 - C_5 , linear or branched, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, C_1 - C_4 alkyl, linear or branched when possible, C_1 - C_4 alkoxy, linear or branched when possible;

C_1 - C_4 perfluoroalkyl, linear or branched when possible, for example trifluoromethyl; nitro, mono- or di- (C_{1-4}) alkylamino;

R_1 and R_2 taken together are the dioxymethylene group, with the proviso in the formula Ib) that R_1 cannot be $OCOR_3$ in position 2 when R_3 is methyl;

nI is an integer and can have the values 0 or 1;

preferably in Ia) R_1 is acetoxy, preferably in ortho position with respect to the $-CO-$ group, R_2 is hydrogen;

preferably in Ib) $R_3 = CH_3$, $nI = 0$;

preferably $R-COOH$ is the acetylsalicylic acid;

said process comprising the following steps, generally carried

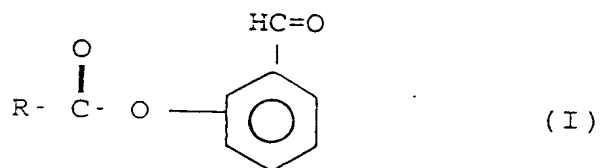
out in the presence of a solvent inert under the reaction conditions:

(1) reaction between the acid halide $R-C(O)-X_I$ wherein:

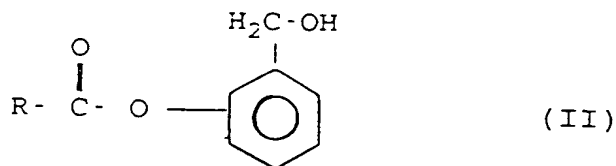
X_I is an halogen selected between Cl and Br,

R is a radical as above defined,

in the presence of a base, with an isomer of the hydroxy-benzaldehyde, i.e., wherein the hydroxyl group can be at ortho, meta or para position, with formation of a (carbonyl)phenyl ester (I):



(2) selective reduction of the aldehydic group of compound (I) with formation of an (hydroxymethyl)phenyl ester (II):

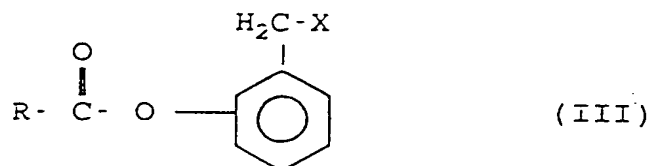


(3) reaction between the (hydroxymethyl) phenyl ester of formula (II) with:

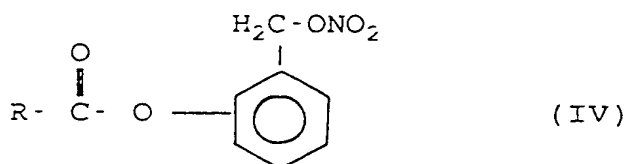
a) SOX_2 , X being an halogen selected between Cl and Br, with formation of an (halogenomethyl)phenyl ester of formula (III), wherein X = halogen,

or

b) tosyl chloride or mesyl chloride with formation of a (tosyloxymethyl)- or (mesyloxymethyl)-phenylester, X being = O-tosyl or O-mesyl in formula (III):



(4) reaction between the compound of formula (III) with an inorganic nitrate salt, the metal cation of which belongs to the group IB or IIB, with formation of the corresponding (nitroxymethyl) phenyl ester



The formation of the (carbonyl)phenyl ester of step (1) can alternatively be achieved by other reactions. For example by reaction of the aspirin derivative of general formula $\text{R}-\text{COOH}$ with a dehydrating agent, such as for example N, N'-dicyclohexylcarbodiimide, in the presence of an aminopyridine derivative N, N disubstituted with alkyl radicals C_1-C_4 (step (1^I)), or with a C_1-C_4 alkylchloroformate in the presence of a base, soluble or insoluble in the reaction medium, as defined hereinafter (step (1^{II})), or with N, N' carbonyldiimidazol (step (1^{III})).

The process object of the present invention allows to obtain products at the required purity degree. Thus it is not necessary to purify the product compounds obtainable after each step. The overall yields are good (50-70%).

In step (1), the aspirin derivative acyl chloride or bromide, prepared from the corresponding compound in the acid form by using known reactants (ex. thionyl chloride, thionyl bromide, oxalyl chloride, oxalyl bromide, PCl_3 , PBr_3), is let react in inert solvents (for example halogenated hydrocarbons such as dichloromethane, trichloromethane; ethers, such as ethyl ether, propyl ether, isopropyl ether, dioxane; esters such as ethyl acetate, propyl acetate, butyl acetate), in the presence of an organic or inorganic base, with an hydroxybenzaldehyde isomer as above defined. Said base can be soluble in the reaction solvent, as in the case of tertiary aliphatic amines of formula $\text{N}(\text{R}_\text{N})_3$, wherein R_N is an alkyl group $\text{C}_1\text{-C}_4$, such as for example tributylamine, triethylamine, diethylmethylamine, trimethylamine; or said base can either be insoluble in the solvent, such as for example in the case of alkaline inorganic salts, for example, potassium carbonate, sodium carbonate, or alkaline metal bases such as NaOH and KOH .

When step 1) is substituted with step (1^I) as above defined, the aminopyridine derivative N, N disubstituted with alkyl radicals $\text{C}_1\text{-C}_4$, used in combination with the dehydrating

agent, is preferably selected for example from dimethylamino pyridine and dibutylamino pyridine; when instead step (1^{II}) is used, the compound C₁-C₄ alkylchloroformate is preferably selected between ethylchloroformate and isobutylchloroformate.

The reaction (2) of selective reduction of the aldehydic group to alcohol can be carried out by hydrogenation with gaseous hydrogen using conventional catalyts supported on carbon, such as for example, palladium, in a solution of the compound of formula (I) in an inert solvent. The reaction temperature is in the range 0-40°C, the gas pressure can range from 1 to 3 atm.

In alternative to the hydrogenation with gaseous hydrogen, reduction of compound (II) can be effected also with other reducing agents, for example inorganic mixed hydrides, such as for example NaBH₄, under the conditions well known to the skilled in the field.

Step (3) is carried out in an inert organic solvent at a temperature in the range 0°-40°C.

The alternative reaction between the alcohol and the tosyl chloride or mesyl chloride is carried out according to the known methods of the prior art.

Step (4) is carried out by adding an inorganic nitrate salt which cation is selected from metals belonging to the Groups IB and IIB, to a solution of the compound of formula (III), wherein X is halogen as above defined, or O-tosyl or O-

mesyl, in an organic solvent wherein said nitrate salt should be soluble, such as for example acetonitrile, tetrahydrofuran. The cation of the salt can be zinc, silver or mercury. Preferably the salt is silver nitrate. The reaction temperature can range between 20° and 90°C.

The synthesis appears to be specific:

when in the process object of the present invention are used as starting compounds other therapeutically active molecules having a reactive carboxylic function, it is found that the corresponding nitroxymethylphenyl esters are obtained with lower yields, as it is shown in the Examples.

The following Examples are given with the only purpose to illustrate the invention and they do not limit the same.

EXAMPLE 1

Preparation of the 2-(acetyloxy) benzoic acid 3-(nitroxymethyl)phenyl ester

EXAMPLE 1a

Preparation of the 2-(acetyloxy)benzoic acid 3-(formyl)phenyl ester

A mixture of 3-hydroxybenzaldehyde (830 g) and triethylamine (8.24 g) in methylene chloride (12.6 l) is kept under stirring, in inert nitrogen atmosphere, cooling at a temperature between -5°C and 0°C. Salicyloyl chloride (1650 g) is added in small portions in an hour. The mixture is still kept under stirring for 15 minutes, then water (10 l) is added and

the phases are separated. The aqueous phase is recovered and apart extracted with methylene chloride (3 l). The organic phases are joined together, washed with a 5% Na_2CO_3 solution (5 l X 2 times) and then with water (5 l X 2 times). The organic phase is dried with magnesium sulphate (2 Kg) in the presence of decolorating carbon (300 g). It is filtered under vacuum and the solvent is evaporated at reduced pressure at a bath temperature lower than 40°C , at last obtaining 1929 g of 3-(formyl)phenyl ester of the 2-(acetoxy) benzoic acid (quantitative yield) m.p. $80-84^\circ\text{C}$. The compound purity determined by HPLC, by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 55/45, was equal to 98.5%.

EXAMPLE 1b

Preparation of the 2-(acetyloxy)benzoic acid 3-(hydroxy-methyl)phenyl ester

The 2-(acetyloxy)benzoic acid 3-(formyl)phenyl ester (1929 g) is dissolved in ethyl acetate (11 l) in the presence of 5% palladium on carbon (290 g) with the 50% of humidity.

The mixture is hydrogenated at room temperature and hydrogen pressure of about 2.5 atm, under stirring. The reaction during the first hour is slightly exothermic and the temperature in the reactor increases up to 35°C . After eight hours fresh catalyst (100 g) is added to complete the reaction. After 12 hours the reactor is discharged, the

catalyst is removed by filtration under vacuum, in nitrogen atmosphere, washing the panel with ethyl acetate (2 l). The organic phases are joined together and are washed with a 5% sodium bicarbonate solution (3 l X 2) and with water (3 l X 2). The organic phase is dried with magnesium sulphate (2 Kg) in the presence of decolorating carbon (100 g). It is filtered under vacuum and evaporated at reduced pressure at a bath temperature lower than 40°C, obtaining 1,850 g of 2-(acetyloxy)benzoic acid 3-(hydroxymethyl)phenyl ester with yield of 95.2%, m.p. 77-79°C. The compound purity determined by HPLC, by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 55/45, is equal to 99.0%.

EXAMPLE 1c

Preparation of the 2-(acetyloxy)benzoic acid 3-(chloromethyl)phenyl ester

To a mixture constituted by 2-(acetyloxy)benzoic acid 3-(hydroxymethyl)phenyl ester (1850 g) and thionyl chloride (5.5 l) kept under stirring, dimethylformamide (5 ml) is added at room temperature and is left under stirring for one hour. At last the thionyl chloride is evaporated at reduced pressure at a bath temperature lower than 40°C. The residual traces of thionyl chloride in the compound are eliminated treating the solid with toluene (2 l X 2), which is then removed by evaporation at reduced pressure at a bath temperature lower than 40°C. The so obtained crude solid is

purified by crystallization with isopropyl ether (30 l), removing by filtration the residue which remains undissolved in the crystallization solvent brought to the boiling temperature.

After cooling and filtration at reduced pressure, a solid is isolated which is dried under vacuum at room temperature, obtaining 1,367 g (yield 69.4%) of 2-(acetyloxy)benzoic acid 3-(chloromethyl) phenyl ester m.p. 71-73°C. The compound purity, determined by HPLC using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 40/60, is 99.0%.

EXAMPLE 1d

Preparation of the 2-(acetyloxy)benzoic acid 3-(nitroxymethyl) phenyl ester

A solution of 2-(acetyloxy)benzoic acid 3-(chloromethyl) phenyl ester (1,367 g) in acetonitrile (8 l) is treated under stirring, sheltered from the light and at room temperature with AgNO_3 (915 g). It is heated up to reflux for two hours and then it is cooled at room temperature and AgNO_3 (115 g) is added. It is heated again at reflux and after 4 hours it is cooled to 10°C; the precipitate (silver salts) is filtered under vacuum and washed with acetonitrile (1 l X 2). The organic phases are joined together and the solvent evaporated under vacuum at a bath temperature lower than 40°C. The residue is dissolved in chloroform (4 l), decolorating carbon (100 g) is added, it is stirred and the organic phase is percolated

on a silica panel (2.5 Kg). The silica is washed with chloroform (10 l).

The organic phases are joined together and are concentrated to small volume at reduced pressure and bath temperature lower than 40°C until in the solution the formation of a precipitate (about 3 l by volume) is noticed. The volume of the solution is maintained constant by continuously feeding isopropyl ether (6 l), continuing the chloroform evaporation at reduced pressure until its complete removal from the organic phase. The organic phase is left under stirring for two hours at the temperature of 20°C. It is filtered under vacuum washing with isopropyl ether (1.5 l) the solid on the filter. After drying under vacuum at room temperature, 1200 g of 2-(acetyloxy)benzoic acid 3-(nitroxymethyl) phenyl ester (yield 80.7%) m.p. 63.5-64°C, are isolated. The compound purity, determined by HPLC by using a LiChrospher® 100 RP 8 column, eluent buffer phosphate pH 8/acetonitrile 50/50, is 99.75%. The final product structure has been confirmed by ¹H-NMR (CDCl₃): 8.22 (1H, dd), 7.66 (1H, td), 7.47 (1H, t), 7.40 (1H td), 7.32 (1H, d), 7.24-7.21 (2H, m), 7.18 (1H, dd), 5.44 (2H, s), 2.30 (3H, s).

The global process yield is 53.3%.

EXAMPLE 2

Preparation of the 2-(acetyloxy)benzoic acid 2-(nitroxymethyl)phenyl ester

The product is prepared according to the procedure described in Example 1, by using as alcohol 2-hydroxybenzaldehyde. By analyzing the final compound obtained by chromatography on a thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitary stain is obtained. The final product structure has been confirmed by $^1\text{H-NMR}$ (CDCl_3): 8.22 (1H, dd), 7.68 (1H, dt), 7.35 (6H, m), 5.40 (2H, s), 2.30 (3H, s). The global process yield is 67.8%.

EXAMPLE 3

Preparation of the 2-(acetyloxy)benzoic acid 4-(nitroxymethyl)phenyl ester

The product is prepared according to the procedure described in Example 1. The used aromatic hydroxy-aldehyde is 4-hydroxybenzaldehyde. By thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitary stain is obtained. The final product structure has been confirmed by $^1\text{H-NMR}$ (CDCl_3): 8.21 (1H, dd), 7.66 (1H, dt), 7.42 (6H, m), 5.40 (2H, s), 2.25 (3H, s). The global process yield is 57.5%.

EXAMPLE 4

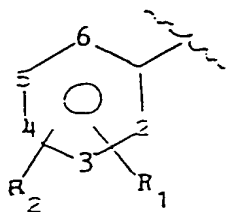
Preparation of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester

The product is prepared according to the procedure described in Example 1. The aromatic hydroxy-aldehyde used in step (1) is 3-hydroxybenzaldehyde. The global process yield is 39.1%. By analyzing the final product by chromatography on

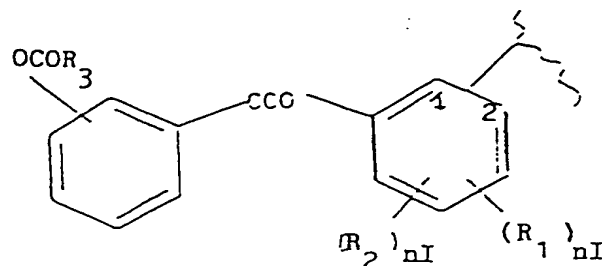
thin layer of silica gel, an unitary stain is obtained. M.p. 115-117°C. $^1\text{H-NMR}$ (CDCl_3): 7.70 (2H, d), 7.49 (2H, d), 7.42 (1H, t), 7.14-7.06 (4H, m), 6.90 (1H, d), 6.70 (1H, dd), 5.42 (2H, s), 3.93 (2H, s), 3.86 (3H, s) 2.48 (3H, s).

CLAIMS

1. A process for obtaining (nitroxymethyl)phenyl esters of aspirin derivatives of formula $R\text{-COOH}$ wherein R is selected from one of the radicals having the following formula:



Ia)



Ib)

wherein:

R_1 is the OCOR_3 group; wherein R_3 is methyl, ethyl or alkyl $\text{C}_3\text{-C}_5$ linear or branched, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, $\text{C}_1\text{-C}_4$ alkyl, linear or branched when possible, $\text{C}_1\text{-C}_4$ alkoxy, linear or branched when possible; $\text{C}_1\text{-C}_4$ perfluoroalkyl, linear or branched when possible; nitro, mono- or di- $(\text{C}_1\text{-C}_4)$ alkylamino;

R_1 and R_2 taken together are the dioxymethylene group, with the proviso that in the formula Ib) R_1 cannot be OCOR_3 in position 2 when R_3 is methyl;

nI is an integer and can take the values 0 or 1;

said synthesis process comprising the following steps:

- (1) reaction between the halide $R-C(O)-X_I$ (A) wherein:
 X_I is Cl, Br, R being a radical as above defined,
with an isomer of the hydroxy-benzaldehyde, in the presence of a base, with formation of a (carbonyl)phenyl ester;
- (2) reduction of aldehydic group of the (carbonyl)phenyl ester with formation of an (hydroxymethyl)phenyl ester;
- (3) reaction between (hydroxymethyl) phenyl ester of formula (II) with:
 - a) SOX_2 , X being an halogen selected between Cl and Br,
 - or
 - b) tosyl chloride or mesyl chloride ;
- (4) reaction between the ester isolated at the previous step with an inorganic nitrate salt, which metal cation belongs to the group IB or IIB, with formation of the (nitroxymethyl) phenyl ester.

2. A process according to claim 1, wherein the formation of the (carbonyl)phenyl ester expected in step (1) is alternatively carried out by reacting the aspirin derivative of formula $R-COOH$ with a dehydrating agent in the presence of an aminopyridine derivative N, N di-substituted with alkyl radicals C_1-C_4 , or of a C_1-C_4

alkylchloroformate in the presence of a base, or with N, N' carbonyldiimidazole.

3. A process according to claim 1, wherein the nitrate used in step (4) is silver nitrate.
4. A process according to claims 1-3, wherein the aspirin derivative of formula R-COOH is the acetylsalicylic acid.
5. (Hydroxymethyl)phenylester of aspirin derivatives of formula R-COOH, wherein R is as above defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/00353

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C203/04 C07C201/02 C07C69/90 C07D209/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K BOWDEN ET AL: "Prodrugs - Part 1. Formylphenyl esters of aspirin" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY. CHIMICA THERAPEUTICA., vol. 32, no. 12, 1997, pages 987-993, XP002138161 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS., FR ISSN: 0223-5234 page 988	1
A	WO 97 16405 A (NICOX SA) 9 May 1997 (1997-05-09) cited in the application example 3	1,3,4
A	WO 92 01668 A (ITALFARMACO SPA) 6 February 1992 (1992-02-06) example 8	1,3,4
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 May 2000

Date of mailing of the international search report

14/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bonnevalle, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/00353

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B HELFERICH: "Zwei desmotrope Formen des 2-Benzoyloxy-benzylalkohols, ein neuer Fall von Ring-Ketten-Tautomerie" CHEMISCHE BERICHTE., vol. 83, 1950, pages 567-571, XP002138162 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0009-2940 page 569	1
A	R GRICE ET AL.: "Cytotoxic Compounds. Part IV. Substituted benzyl halides" JOURNAL OF THE CHEMICAL SOCIETY., 1963, pages 1947-1954, XP002138163 CHEMICAL SOCIETY. LETCHWORTH., GB page 1950 -page 1951	1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/EP 00/00353

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9716405	A	09-05-1997	IT MI952263 A	30-04-1997
			AU 709338 B	26-08-1999
			AU 7495096 A	22-05-1997
			BR 9611175 A	30-03-1999
			EP 0871606 A	21-10-1998
			HU 9802986 A	28-04-1999
			JP 11514636 T	14-12-1999
			US 6040341 A	21-03-2000
WO 9201668	A	06-02-1992	IT 1243367 B	10-06-1994
			AT 118478 T	15-03-1995
			AU 8097491 A	18-02-1992
			CA 2087442 A	27-01-1992
			DE 69107459 D	23-03-1995
			DK 540544 T	26-06-1995
			EP 0540544 A	12-05-1993
			ES 2056783 T	16-10-1994
			GR 93300079 T	31-08-1993
			HU 213405 B	30-06-1997
			NO 930215 A	22-01-1993
			US 5589490 A	31-12-1996
			US 5366992 A	22-11-1994